Identifying viable regulatory and innovation pathways for regenerative medicine

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Research Paper

Identifying viable regulatory and innovation pathways for regenerative medicine: a case study of cultured red blood cells

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The creation of red blood cells for the blood transfusion markets represents a highly innovative application of regenerative medicine with a medium term (5–10 year) prospect for first clinical studies. This article describes a case study analysis of a project to derive red blood cells from human embryonic stem cells, including the systemic challenges arising from (i) the selection of appropriate and viable regulatory protocols and (ii) technological constraints related to stem cell manufacture and scale up to clinical Good Manufacturing Practice (GMP) standard.

The method used for case study analysis (Analysis of Life Science Innovation Systems (ALSIS)) is also innovative, demonstrating a new approach to social and natural science collaboration to foresight product development pathways. Issues arising along the development pathway include cell manufacture and scale-up challenges, affected by regulatory demands emerging from the innovation ecosystem (preclinical testing and clinical trials). Our discussion reflects on the efforts being made by regulators to adapt the current pharmaceuticals-based regulatory model to an allogeneic regenerative medicine product and the broader lessons from this case study for successful innovation and translation of regenerative medicine therapies, including the role of methodological and regulatory innovation in future development in the field.

Introduction: background to the case study

Regenerative medicine (RM) is a highly promising area for the development of novel therapies with the capacity to solve intractable human health problems. Applications range from one-off autologous therapies where a patient's own cells are extracted and cultured before being transplanted back into the same patient, to allogeneic therapies requiring large scale culturing of cells from a single donor that are then provided to many patients. Autologous therapies, akin to the 'surgical procedure' model (low volume/high cost), are currently delivering successful treatments in several areas. Allogeneic therapies, the subject of this paper, are much more challenging [1]. They are being developed for widespread distribution to large numbers of patients and will be cultured in large scale production facilities, requiring levels of scale-up that are currently very difficult to achieve. However, successful development of allogeneic therapies will be needed if regenerative medicine is to fulfil its promise to meet future healthcare needs on a significant scale. Such products are analogous to a pharmaceutical production model (high volume/widely distributed product for large patient populations) with its expected economies of scale.

The Bloodpharma case study described in this paper is an important test case for the future development of allogeneic therapies. It involves the industrial scale production of cultured red blood cells (RBCs) from pluripotent stem cell lines and aims

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eventually to meet the need for new sources of blood products arising from problems in the current supply chain, risks of transfusion transmitted infection and risks associated with immune responses for patients requiring repeat transfusions. It illustrates many of the uncertainties faced by allogeneic RM therapies: identifying and developing viable product development pathways and funding models [2–4]; related scientific, technological and regulatory challenges [5] and bio-processing/scale up options [6,7]; difficulties in implementing the regulatory system based on the pharmaceutical model adopted for RM products [8–11]; and reimbursement and clinical uptake [12].

Socio-economic research on RM-related issues has so far been done from a range of mono-disciplinary or narrowly focused perspectives. These include the development, standardisation and regulation of early stage stem cell research [13,14]; the storage and handling of new types of biological material [15]; ethical traditions and international differences in the approval of stem cell research [16,17]; the politics of stem cell research and public engagement [18,19]; socio-economic expectations of stem cell treatment [20,21]; the known and potential risks of cell therapies and the implications of proposed regulations for late stage innovation [22–25]; and the manufacturing, scale up, and supply challenges in delivering RM as a commercially viable technology [6,7,26,27].

This paper describes the first major application of a novel interdisciplinary approach to life science innovation (Analysis of Life Science Innovation Systems (ALSIS)) [2], adopting a strategic mapping approach to the projection of development pathways for cultured red blood cells, and demonstrating how social and natural science collaboration can deliver important new insights on life science innovation processes. This interdisciplinary and systemic approach allows consideration of interactions across the science/innovation/policy/regulatory nexus to deliver insights that would not otherwise emerge from a conventional socio-economic analysis and to support better decision making by both innovators and policy makers. By linking the regulatory pathway with the manufacturing/scale-up pathway for this product, and illustrating where the two must successfully align, this article is the first systemic foresight analysis of a novel product in early stage development and provides data that are relevant to, and can inform, broader debates about the development of regenerative medicine products.

Our analysis focuses on challenges to the development of the Bloodpharma product arising from: scientific and technical uncertainties; the regulatory system; manufacturing/scale up challenges; and the impact of all these factors on potential markets and the overall commercial viability of the product.

Research method and data sources

The Blood Pharma Case Study – target market for the product

The Bloodpharma project is a strategic partnership funded by the Wellcome Trust and the Scottish Funding Council to deliver a stem cell-derived blood product (http://www.wellcome.ac.uk/news/media-office/Press-releases/2009/WTX054309.htm). This was one of three case studies considered for the REALISE project [2], funded by the UK Economic and Social Research Council (ESRC) through the Technology Strategy Board. The authors of this paper (Innogen and Bloodpharma Project researchers) worked together to map the future product development pathway envisaged for the Bloodpharma therapy. This project, and our analysis, were completed in 2012 and do not cover subsequent developments that are resolving some of the important uncertainties described here.

Global demand for blood for routine transfusion is approximately 100 million units/year, each requiring 2.5 × 10e12 RBCs. Previous attempts to develop 'artificial' blood have failed due to problems with toxicity and manufacture [28,29] but stem cell science offers the potential successfully to differentiate RBCs for clinical use. However, achieving this scale of production to clinical grade GMP standard at a price that is competitive with that of a standard unit of blood is currently a challenging aim. The Bloodpharma project has focused initially on the beta-Thalassemia market where patients suffer problems with iron loading, for which drugs with unpleasant side effects must be administered [30,31]. The cultured RBCs could reduce reliance on donor recruitment, and the risks of transfusion transmitted infection and of immune incompatibility, through provision of a 'universal donor' blood group (such as O Rhesus D negative and Kell negative). Since the product will consist of a homogeneous population of young red cells (reticulocytes), the cells should have a longer life span once transfused. This would be of benefit to beta-thalassemia patients, who may require fewer transfusions and therefore experience less iron loading. These benefits would justify a price premium for the initial product, perhaps enabling it to cover the cost of meeting the technical and regulatory constraints described here.

The ALSIS approach

The method we developed for this project, Analysis of Life Science Innovation Systems (ALSIS) [2] uses a strategic mapping approach to project future business models and product development pathways (defined as the full range of activities required to bring a product from conception to end use, including design, production, marketing, distribution and support to the final consumer). These factors, broadly speaking under the control of the innovator, are embedded within an innovation ecosystem that includes the economic, regulatory, societal and political contexts that are beyond the control of the innovator, with either positive or negative impacts on the product business plan. For the Bloodpharma project, critical decision points within the product development pathway arose from the scientific and technological challenges of differentiating sufficient quantities of RBCs from stem cells meeting clinical grade GMP standards for different stages of pre-clinical and clinical testing; and the implications for product development and regulatory science of targeting the niche Thalassaemia market. The main innovation ecosystem components discussed in this paper are the regulatory system and the challenge of meeting requirements related to the use of conventional preclinical animal models and to the conduct of human clinical trials.

The strategic maps in Figs 1–4 were developed using Banxia Decision Explorer software (http://www.banxia.com/dexplore/) and are based on discussions with case study participants during interviews and workshops. They consist of a series of 'concepts', short statements, each representing an action that leads, as shown by the arrows on the map, either causally or temporally to the next

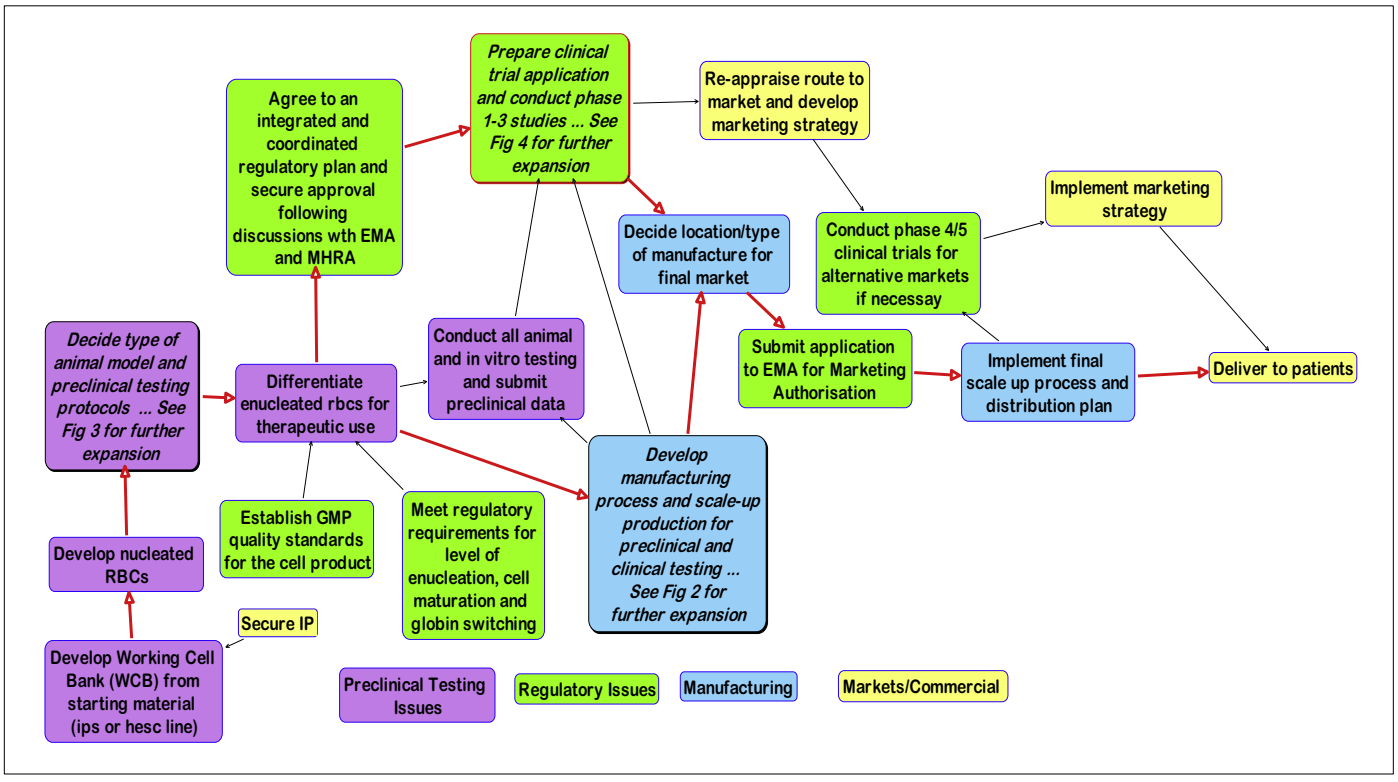

FIGURE 1

Value chain critical points.

action or actions. In this case, the concepts are either components of the projected product development pathway or elements of the innovation ecosystem. The red arrows delineate the expected critical path to market and black arrows represent Bloodpharma or other actor impacts that are beyond the critical path. The concepts are colour coded: purple (preclinical testing); green (regulation); blue (manufacturing); and yellow (markets/commercial outcomes). Concepts with bold/italicized typeface and a thick border are placeholders linking to the other figures that give more detail on a particular strategic issue. The direction of the arrows is

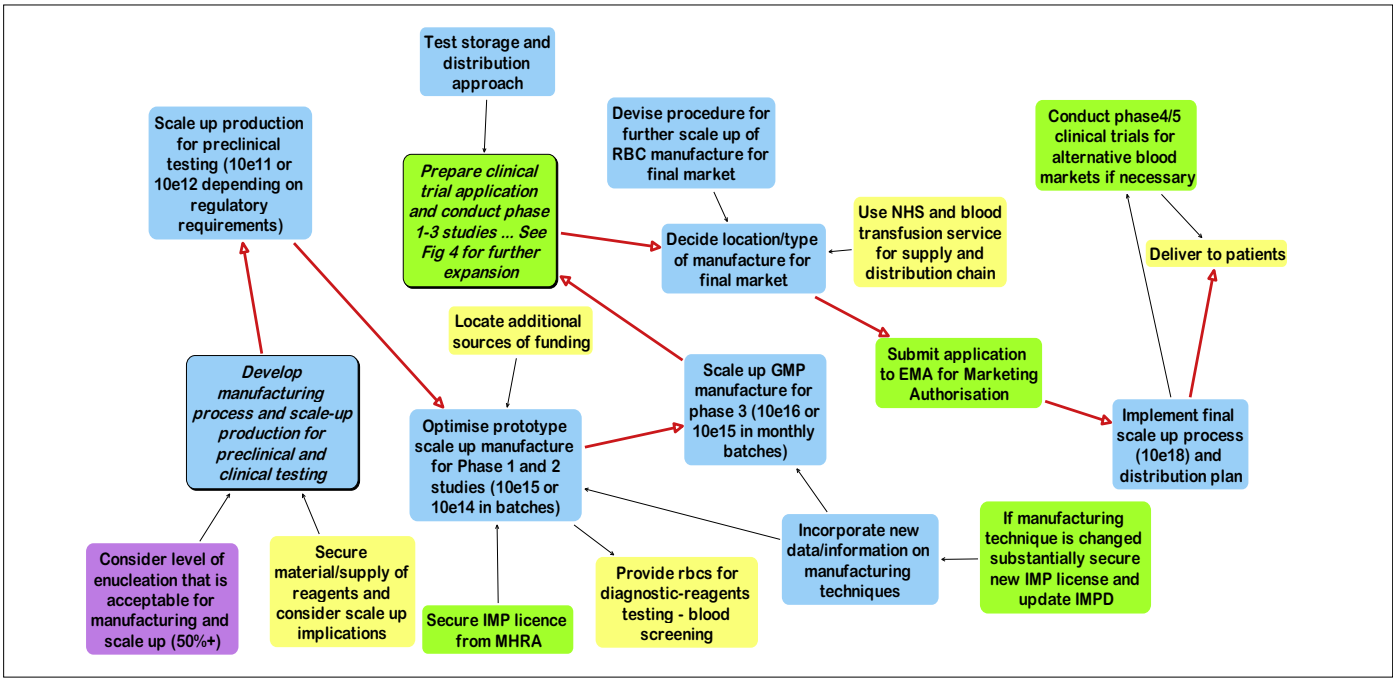

FIGURE 2

RBC manufacturing pathway.

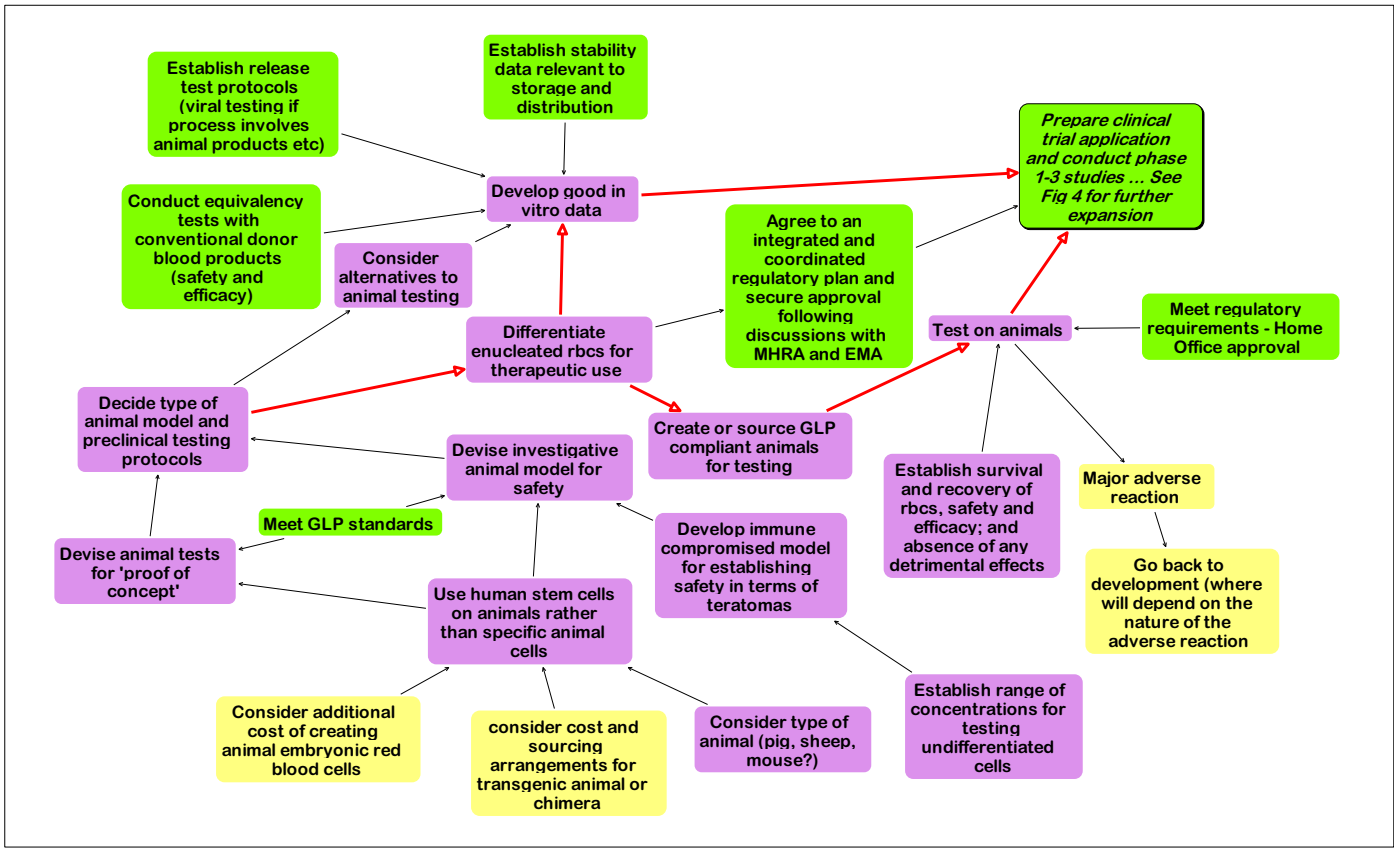

FIGURE 3

Pre-clinical testing map.

generally from left to right, with parallel processes and feedback loops demonstrating the non-linearity of the process. Figs 1–4 are summary versions of the more detailed strategic maps developed for the case study [2]. Figure 1 is an overall value chain, showing the parallel regulatory and manufacturing paths for the product, from the development of a working stem cell bank and the creation of enucleated RBCs through to the projected Thalassemia patient market. Figs 2–4 expand on manufacture and scale-up aspects of the product development pathway and preclinical and clinical regulatory requirements.

Data collection

Data were gathered in 2010–2012 from five workshops (4–8 participants in each), three interviews with senior people involved in the Bloodpharma project, and one interview with a former regulator. Key informants included those responsible for commercialisation/financing, regulatory affairs, GMP and manufacturing, and basic scientific research. Published data and 'grey literature' also informed our analysis. Workshops and some interviews were recorded and transcribed to enable us to capture detailed qualitative and quantitative information from which to construct the strategic maps. Development and refining of these maps was an on-going process throughout the project, informed by meetings and discussions with the Bloodpharma team, and also with external stakeholders through a series of meetings organised by the lead partners in the REALISE project, the Scottish Stem Cell Network.

Research results

Scientific and technological challenges

Figure 1 illustrates the sequence of decisions related to the scientific and technical challenges in developing the cultured product, showing the critical points in the overall pathway at which manufacturing and scale-up decisions would need to be finalised and where such decisions would interact with the regulatory system. The first concepts at the start of the critical path, obtaining a starting cell line and developing a working cell bank bring up the question of the expected starting material. Between 2010-12 the project was using human embryonic stem cell (hESC) lines as the starting material, but the long-term plan was to use induced pluripotent stem cell (iPSC) lines. Factors favouring that choice included: the requirement for open-source hESC banking in the UK [32]; and the European Brustle patent decision, limiting the patentability of hESC-derived products in Europe [33,34]. This is an example of how policy and regulatory decisions can rapidly transform product development strategies. In addition, a technological justification for switching in future to iPSC lines was that the cultured blood should ideally be type O RhD-negative, and no GMP-grade hESC lines of that blood type were available.

Following the logic of the pathway in Fig. 1, the developers should, where possible (e.g. except where hESCs have been involved), secure intellectual property on the cell lines and on components of the production process. Developers also need to meet clinical grade GMP requirements for cells and facilities. At the time of the REALISE project, the Bloodpharma team was in the process of

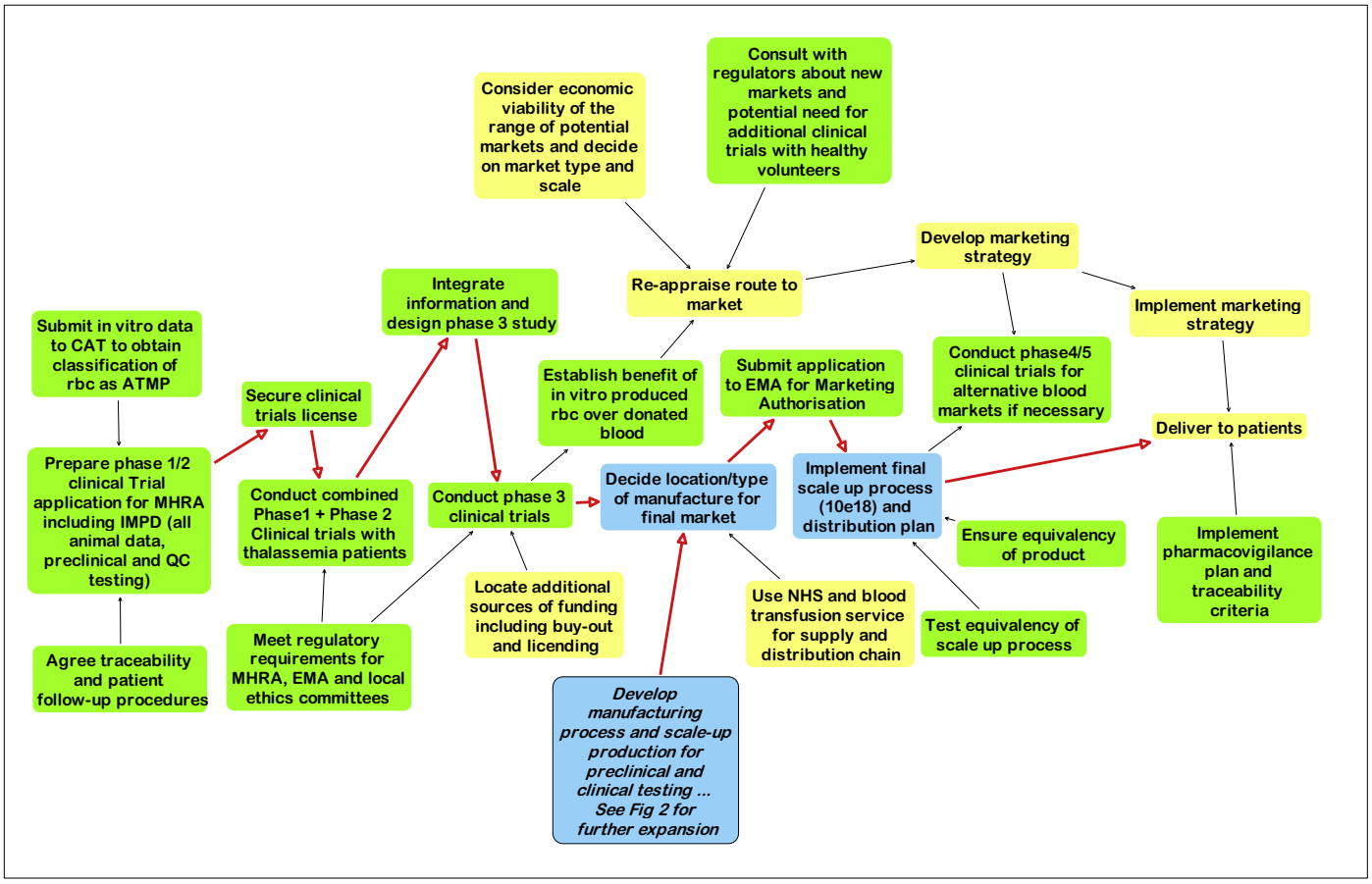

FIGURE 4

RBC clinical trial map.

attempting to derive enucleated RBCs from the nucleated red blood cells that had been created in the laboratory as illustrated in the purple boxes on the left hand side of Fig. 1. The target product was one that exhibited: definitive erythroid lineage cells (including globin switching); normal oxygen carrying capacity; morphology that resembles normal RBCs, a deformability profile that matches the natural product; and output scale-up to approximately 10e16 fully matured cells by the time the project reached Stage 3 clinical trials. These enucleated RBCs were expected to carry a reduced risk of adverse immunogenic response.

Cell enucleation, cell maturation and globin switching (switching from foetal to adult haemoglobin) were always going to be the most urgent technical and scientific challenges facing the Bloodpharma team in the early stages of product development. Globin switching is important because different haemoglobins (embryonic, foetal and adult) have different oxygen dissociation curves, which can impact on the efficacy of the final product. Beyond the preclinical challenges, the product development map splits into parallel regulatory and manufacturing pathways, as discussed in more detail below.

Clinical grade GMP production and scale-up

The critical path in Fig. 2 follows manufacturing and scale-up decisions, from preclinical and clinical testing through to distribution/storage. The need to achieve very significant degrees of scale-up to clinical GMP standard is a major challenge in developing allogeneic stem cell therapies [35], although some of the uncertainties are being reduced over time [7]. As shown on the left hand side of Fig. 2, the large scale production of enucleated RBCs would require a reliable, cost-effective supply of reagents and the cost of goods would need to decline significantly in future if allogeneic therapies are to be viable.

The phased scale-up of production capability for preclinical and clinical testing was a significant challenge for the eventual commercial production of cultured RBCs as for any allogeneic product. If economies of scale can be achieved, the product would eventually benefit from having a well-established, well-regulated route to market via the blood transfusion service's sophisticated supply chain. However, even for the niche thalassemia market, the need to achieve significant step changes in production technology was considered a make-or-break issue.

Key choices on this part of the pathway were: the location of production facilities; development of sufficient production capacity to meet the requirements for preclinical testing and clinical trials; technologies for scale-up; and cost of goods for media and stem cell growth factors. There was continuing uncertainty about the number of tests required at each regulatory stage and hence the number of cells needed, creating inherent risks to the project at four points on Fig. 2, related to these regulatory decision points.

1. Scale-up for preclinical testing was estimated to require approximately 10e11 or 10e12 cells (provided in small batches)

depending on regulatory requirements, which could be achieved using the current manufacturing process.

2. Optimised prototype scale-up for the expected phase 1/2 compressed clinical trial would require approximately 10e15 cells which would produce about 1000 units of blood. While this is a total figure, the cells could not be manufactured in a single batch because of the limited life span of the product. The suggested approach was to manufacture monthly batches of approximately 10e14 for these clinical trials. Data on manufacturing and scale-up processes would need to be included in the clinical trial application to the Medicines and Health Care products Regulatory Agency (MHRA), including the Investigational Medicinal Products Dossier (IMPD). An MHRA manufacturer licence for investigational medicinal products (MIA/IMP) would also be required. At this stage, there was also a perceived opportunity to provide RBCs for diagnostic reagent testing or blood screening, creating a potential early revenue stream. The Bloodpharma team expected to make the decision on whether to continue with the GMP hESC line or switch to a GMP iPSC line in 2016, prior to commencing the phase 1/2 clinical trial.
3. Scale up for phase 3 clinical trials would require approximately 10e16 RBCs (or 10e15/month). As in the previous stage, any new data on manufacturing techniques would need to be integrated into plans for future batch processing techniques. However, if the manufacturing technique was changed substantially the IMPD would need to be updated.
4. Considering the thalassemia market, there are approximately 1000 UK based thalassemia patients and they would use approximately 50,000 units ($5 \times 10e16$ RBCs) per year. In Europe there are approximately 70,000 thalassemia patients, requiring 10e18 per year or 10e17 per month. At this stage, scale-up to 10e18 RBCs (approximately a million units) per year would provide sufficient supply for thalassemia markets and for subsequent clinical trials for alternative blood markets. At this stage, as for the previous stages, it would also be necessary to demonstrate equivalency of the scale-up process and final product.

If at any of these stages the ability to scale-up to the required number of cells became technologically unachievable or unviable due to the cost of goods (relative to the price that can be charged for the product), or the product failed to meet regulatory requirements, the product would be at risk of failure. Products such as this, developed by organisations without the resources of a multinational company, have very little capacity to accommodate any serious delay, creating a requirement for a viable exit strategy. This is a problem for most stem cell therapies currently in development. The technology required for these levels of scale-up was not available at the time of the study but given sufficient time and resource it was assumed that the required levels of scale up would be technologically feasible.

During the cell differentiation process the rate of maturation and proliferation of the cell population varies at different steps and the manufacturing process requirements (media, cytokine, culture density, metabolic turnover) also vary. The biggest step forward was expected to come from being able to grow cells in the later stages of differentiation at very high cell density, reducing the total volume in those steps when the cell numbers are greatest. This would be equivalent to the technological improvements that have been made over the last 10 years for antibody and protein therapeutic production in Chinese Hamster Ovary (CHO) and similar cell lines. However, success would be dependent on fully understanding the cell requirements and having the capacity to modify or supplement conditions appropriately.

While the level of public sector investment was expected to be sufficient to take the product up to the stage of phase 1/2 clinical trials, a phase 3 trial and final market delivery, even for the thalassemia market, was estimated to require tens of millions GBP in commercial investment. Furthermore, serving the thalassemia market would have implications for storage and distribution systems as the largest numbers of patients are outside of the UK. Location of production and distribution facilities, and storage and distribution strategies (blue and yellow concepts on the right hand side of Fig. 2), would therefore have to be aligned with initial and potential future markets (top part of Fig. 4: green and yellow concepts).

Regulatory systems

As Fig. 1 showed, there are close interactions between the manufacturing and scale-up path adopted and the regulatory system to which the product will be subject. One of the main issues raised by this case study was the appropriateness of a regulatory system that is based on a conventional pharmaceutical regulatory model. The key decision points along the regulatory pathway for the cultured blood product were preclinical animal testing and Phase 1/2 human clinical trials.

The competent authorities governing regenerative medicine therapies in the UK are the MHRA and the Human Tissue Authority (HTA), in addition to the Human Fertilisation and Embryology Authority for approval to work with hESCs. They are responsible for applying the European Directives that provide the legal basis and regulatory oversight for RM products.

1. The EU Tissues and Cells Directives (Directive 2004/23/EC and two technical directives -2006/17/EC and 2006/86/EC), are transposed into UK law through the Human Tissues (Quality and Safety for Human Use) Act[1], the HTA being the UK competent authority. They deal with products derived from tissues or cells intended for human application, such as stem cells for haematopoietic reconstitution, covering standards for quality, safety and procurement of cell lines and GMP. Together, these Directives ensure potential risks in research and development are managed effectively.
2. The Clinical Trials Directive (2001/20/EC) provides a legal framework for good clinical practice and governance of clinical trials in Europe, and therefore the protection of human research subjects. The Good Clinical Practice 2005/28/EC Directive further ensures that trials are conducted according to best practice.
3. The Advanced Therapy Medicinal Products (ATMP) Regulation (EC Regulation 1394/2007) provides a centralised approval

[1] SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 SI, 2007: 1523 http://www.legislation.gov.uk/uksi/2007/1523/contents/made.

process for advanced therapies, covering quality, safety, efficacy and post authorisation vigilance. It also includes special incentives for SMEs. Advanced therapies are defined as '... innovative, regenerative therapies which combine aspects of medicine, cell biology, science and engineering for the purpose of regenerating, repairing or replacing damaged tissues or cells'. The ATMP Regulation plays an important role in managing risk and judging efficacy for novel therapies such as stem cells and tissue-engineered products. Its 'risk based approach' [36] aims to promote health protection, facilitate innovation and provide a degree of legal certainty whilst allowing for technical flexibility.

Key components of the regulatory system for product efficacy and safety are:

a. A central marketing authorisation procedure for advanced therapy products requiring marketing and/or manufacturing authorisation, including autologous and allogeneic human tissue engineered products (hTEPs). Any cells substantially manipulated, modified or based on an 'engineered process' are subject to the regulation, but unmodified cells used in transplants or for homologous use (such as bone marrow transplants, peripheral blood and cord blood HSC transplantation) are excluded. The emphasis of the approval process is on demonstration of quality, safety and efficacy of treatment, so these cell-based therapies are essentially treated as medicinal, pharmaceutical products.
b. A Committee for Advanced Therapies (CAT) within the European Medicines Agency (EMA) to develop criteria and guidelines for product evaluation, drawing on Community-wide expertise.
c. Technical and risk management requirements to ensure quality, safety, efficacy, traceability and post-marketing surveillance.
d. Incentives built into the procedures to support innovation in small and medium sized enterprises (SMEs) through fast-track assessment and free advice, given that opaque and lengthy regulatory procedures, coupled with a lack of scientific expertise in some authorities, were making it difficult for SMEs to bring human tissue-engineered products to market. This excludes non-commercial organisations such as the UK National Health Service (NHS).
e. The Regulation distinguishes between hospital-based and commercial research, and specifies different regulatory requirements for hospitals growing cells for autologous treatments on a non-routine basis. In the UK, the 'hospital-exemption' permits medical doctors or surgeons in hospitals to provide treatments to patients that have not been approved for trial or full licensing. This has not been implemented in a common way across Europe and it would not apply to the cultured blood product.

This centralised procedure for advanced therapies aims to reduce the risks and uncertainties faced by developers of such therapies, but it does impose high regulatory hurdles for safety, efficacy, quality and post-marketing surveillance. However, as the Bloodpharma product will initially be developed for Thalassemia patients, it is likely to qualify as an Orphan indication, reducing some of the regulatory costs. Nevertheless the centralised procedure, and the spirit of the ATMP regulation, is based on a pharmaceutical model of regulation and its approach to judging safety and efficacy of ATMPs, particularly preclinical and clinical testing. Handling living material, maintaining its integrity and freedom from contamination and delivering it to patients requires different facilities and skill sets from those of the pharmaceutical innovation system and these challenges are being met initially by the smaller companies or public and private health service providers that are at the forefront of developing the technology, as in the case of the Bloodpharma team.

The principal regulatory questions on safety and efficacy of cultured RBCs are: the appropriateness of animal models for preclinical testing, and probable future regulatory requirements at this stage of development; and requirements for the design and execution of clinical trials, first for a niche Thalassemia market and then for other blood-related markets and/or general transfusion.

Preclinical regulatory requirements

The Bloodpharma team expected that both in vitro characterisation of the product and proof of low risk of tumourgenicity would be required, but there were no good animal models of human RBC transfusion. Therefore, the best option was considered to be to test for tumorigenicity from any residual hESC in a NOD-SCID knockout mouse [37] and test for recovery and survival of red cells after transfusion into a NOG mouse to demonstrate comparability with donated red cells.

Figure 3 illustrates the future decision points from establishing an animal model (for both proof of concept and safety) and testing protocols, to preparing the clinical trial application form. The Bloodpharma team would need to define the quality control assays and establish general quality standards for the cultured blood product, in line with conventional regulatory requirements for preclinical R&D and the IMPD application (see left side of Fig. 1 and green concept statements around ''in vitro data'' at the top of Fig. 3).

Uncertainty about the regulatory requirements for pre-clinical testing had still not been resolved during our project, yet decisions made then would have implications for future product development and the ability to take the product into a phase 1 clinical trial. Figure 3 illustrates the development stages for animal and non-animal preclinical work and maps the available options and associated uncertainties. In deciding the type of animal model and test protocols for proof of concept and safety testing, a number of options were available with various resource and cost implications.

Case study participants considered it unlikely that regulators would demand prohibitively time consuming and expensive animal studies, for example, creating animal red blood cells from an embryonic stem cell line or creating transgenic animals or chimeras (two yellow concepts at the bottom of Fig. 3), but an immune-compromised animal model could be required to establish a safety profile for the product. However, use of a homologous animal model would not test the same medicinal product as the human stem cell-derived cultured blood and, even in the latter case, a question remains as to whether the comparison would be relevant to the safety and efficacy of the product in humans. This is a key problem for regenerative medicine products that the regulatory system in Europe has not yet been able to fully resolve.

Discussing these issues, the European Committee for Advanced Therapies, which provides technical advice on behalf of the European Medicines Agency (EMA), stated: 'the only relevant species

for testing human cells–when all aspects including receptors, cytokines and micro-environment are considered–is the human being itself.'[38; p. 197]. Nevertheless, the CAT has also argued that there are safety related aspects of cell therapies that can only be addressed in preclinical animal models, including evaluation of bio-distribution by invasive techniques or testing tumorigenic potential with batches of the product cultured beyond specification [38; p. 197].

The Bloodpharma team engaged early with the regulators to discuss options for preclinical testing and this may enable them to avoid extensive and potentially inappropriate animal testing requirements. As illustrated on the left hand side of Fig. 3, an evidence-based case for alternatives to animal testing must be made and the team needed to establish robust in vitro data and to present a strong scientific justification for its relevance and use in the clinical trial dossier (IMPD) that would eventually be submitted to the MHRA/EMA. The MHRA and EMA assess each product on a case-by-case basis, considering the balance between risk and benefit. The need for, and type of, animal testing should be assessed for comparability to the clinical situation and the science. As there are currently no good animal models for blood transfusion, the Bloodpharma team would need to make a case for the animal and in vitro preclinical work that can realistically be delivered, with the caveat that their value will be limited. For animal data, murine models of intravenous blood transfusion can be used to explore cell recovery and survival, and testing of enucleated RBCs in a small animal model was expected to be required for assessing risk of tumorigenicity. In vitro data were expected to include cell numbers, morphology, haemoglobin content, nucleated cell content, rheology, oxygen dissociation and antigen expression. Animal testing continues to be held as a fundamental preclinical standard and developers of innovative products must consider early in the development process what regulators are likely to find acceptable as an appropriate animal study.

If the regulatory requirements for preclinical studies are limited to safety studies in a small animal model, accompanied by in vitro data, the preclinical work was expected to cost approximately £250,000 and take 6–12 months to complete. However, if regulators did insist on a large animal study, and more extensive testing protocols for safety and efficacy (with the limitations outlined above), the time and cost could escalate substantially and pose a threat to the long term viability of the project, and certainly the ability of the team to reach the stage of human clinical trials. Indeed, members of the Bloodpharma team stated that there is no precedent for a successful large animal model of human red cell transfusion. Figure 3 illustrates the greater level of complexity, uncertainty and potential costs around animal testing (the bottom half of the map), as opposed to in vitro data (top portion of the map). This raises the question whether there is scope to rethink the role of animal studies in the preclinical requirements for some regenerative medicine therapies, and to give much greater weight to in vitro techniques, to provide innovators with a very clear and unambiguous route to first clinical trials.

Clinical trials

The beta-thalassemia target market chosen for the Bloodpharma project was considered likely to be amenable to Orphan Medicinal Product regulation, with the attendant benefits of extended market exclusivity, fee reductions and protocol assistance. As a small market, the volume of product required to conduct first in human studies in a few patients would also be much lower than if the target market was general transfusion, when first clinical studies would require a large number of healthy volunteers.

Figure 4 illustrates the key regulatory steps from preparing the clinical trial application, through the completion of first in human studies to phase 3 clinical trials and beyond to the clinic. It includes some of the market related decisions and uncertainties that may be relevant to late stage product development. Beyond the preclinical work outlined in Fig. 3, case study participants developed a regulatory plan to cover three elements: (i) obtain from the CAT classification of the end-product as an ATMP, (ii) prepare for a combined phase 1/2 Clinical Trial Application for the MHRA (left hand side of Fig. 4), including the IMPD (data on manufacturing, testing, stability; and animal, preclinical and quality control testing), and (iii) agree traceability standards with regulators, establish the required patient follow-up period and specify subjects for the phase 1 trial.

For the beta-thalassemia market, the phase 1/2 compressed clinical trial was expected to be conducted on patients rather than healthy volunteers. However, this would be subject to approval from regulators based on the preclinical data. The number of patients required was expected to be relatively low (n50), with less than 10 being involved in the first studies. This would enable the trial to take place in the UK, which would be less costly than organising overseas trials. This trial would look primarily at product safety (identifying any adventitious agents present or abnormal glycosylation) and also begin to collect data on efficacy to feed into the design of the phase 3 trials. The phase 1/2 study is a make-or-break step for the therapy. It highlights the importance of getting clarification on the regulatory requirements as early in development as possible, and planning a robust regulatory strategy for full product development, as summarised in Fig. 4.

Phase 3 trials require demonstration of product superiority, or at least equivalence of performance, compared to conventional donor blood. For thalassemia patients, the team expected that the cultured blood product would perform better than conventional donor blood. The reason for this is that there will be greater consistency in maturity of the RBCs and, perhaps more crucially, they will be consistently younger and therefore predicated to have a longer life span post-transfusion, so less may need to be transfused for the same clinical benefit. Case study participants did not expect the clinical trial regulatory route to a thalassemia market to raise any prohibitive surprises. However, the potential need for additional data to gain marketing authorisation for other blood markets such as general transfusion generates greater uncertainty about the regulatory route to market illustrated on the right side of Fig. 4.

The health economics and reimbursement models will ultimately determine the viability of the option to expand into different markets, and will shape both marketing and manufacturing strategies. Beyond the phase 3 trial, Figs 1,4 are more speculative and liable to change than in earlier stages of development, where there is greater certainty around likely regulatory requirements. However, these uncertainties would only emerge after the product has been shown to be safe and effective for thalassemia patients and there would then be further options to attract investment to develop the product for additional markets. Furthermore,

the Bloodpharma team would then have stronger evidence of the product's performance and safety from the phase 3 thalassemia trials, when negotiating with regulators on the design and conduct of further trials for additional markets.

Discussion and conclusions: broader lessons for translation of regenerative medicine to the clinic

Two important general discussion points emerge from this case study: (i) related to the innovative capacity of regenerative medicine therapies; and (ii) related to the potential role of interdisciplinary social science methods in supporting innovation processes.

The innovative capacity of regenerative medicine therapies

The Bloodpharma product is a disruptive innovation and a standard-setting exemplar for the future of allogeneic regenerative medicine therapies. It is highly innovative and has eventual mass-market potential as a safe alternative to donated blood, building on more immediate niche applications, for example in thalassemia. This case study has demonstrated the technical and regulatory challenges facing the cultured blood product and their complex interactions, requiring an integrated approach to foresighting future development pathways from a relatively small team of people lacking the resources that would be found in a larger commercial company. Innovators working in information and communications technologies often refer to the existence of a 'first mover advantage'. In this case there seems to be a strong 'first mover disadvantage' in that it falls to the first mover to cope with the regulatory and funding uncertainties at the same time as resolving the scientific and technical problems that will emerge for any highly innovative product.

The regulatory system that governs pharmaceutical products and is now being extended to allogeneic RM therapies has a long history of gradual build-up of measures designed to ensure safety and efficacy of new medicines. The time and cost of meeting these complex regulatory requirements has increased substantially in recent decades [10,39,40] and now only large multinational firms are able to deliver new products to large patient populations. For this reason, for stem cell and other advanced therapies being developed by publicly funded research groups or small companies, regulatory agencies are beginning to recognise the need for new governance structures and are embracing developments in regulatory science to support more cost-effective regulatory systems [41–43]. However, there are continuing difficulties in identifying and exploiting viable routes to market for allogeneic RM products. The efforts of regulators to overcome the hurdles facing RM products are reflected in the EMA setting up the Innovation Taskforce to provide a forum for dialogue, and the MHRA establishing the Innovation Office to help organisations developing innovative products to navigate the regulatory system. However, most attempts to revise regulatory processes are piecemeal and incremental, and do not go far enough in establishing a new approach for RM therapies. The House of Lords (HOL) Report [5] stated that the regulatory system for regenerative medicine in the UK was overly complex and at a European level there is disparity in different regulatory bodies' attitudes to the challenges and how best to meet them. Some experts that submitted evidence to the HOL report noted that the current system requires significant improvement.

Although options are being identified for designing and conducting robust safety and efficacy trials in humans for the cultured blood product, the 'gold standard' double-blind and placebo controlled clinical trials, developed with conventional drug therapies in mind, continues to be the default regulatory requirement. Any alternative, such as adaptive trials or unconventional protocols for recruitment and testing, must be justified on a case-by-case basis, adding to the uncertainty, time and cost of development. Webster et al. [44] question whether standard clinical trials will be appropriate for many regenerative medicine products, and we consider there to be some scope for considering a more radical change to the clinical trial system to facilitate innovation of unconventional therapies, whilst at the same time ensuring the highest levels of safety and efficacy.

There are currently no sufficiently robust solutions to the problem of clinical translation for RM. A strategy that requires investing public money in such risky initiatives is likely to experience difficulties when, as will inevitably happen, some projects fail. This adds to the case for a new approach to regulation that considers systemic interactions across the science/innovation pathway and the potential dual role of regulation in both ensuring safety and fostering beneficial innovation.

Perhaps the most important decision taken by any regulatory body is the initial choice of regulatory precedent for an innovative technology. There are good reasons to make such decisions at an early stage in the development of a new technology, not least because commercial funders will require clarity on this question before making any significant investments. However, the earlier such decisions are taken, the greater the chance that serious implementation problems will arise and regulatory systems generally lack the adaptive capacity needed to avoid the waste of resources that occurs when development is stopped for potentially effective, safe and economically viable products.

Regulatory agencies, in collaboration with scientists, are beginning to develop an understanding of the challenges raised by RM and are interested in novel approaches to regulation such as adaptive licensing and innovative clinical trial design. Clinical considerations are touched upon in an EMA reflection paper on stem cell-based medicinal products [45] and a number of schemes are available in Europe to facilitate new pathways to market, for example under a reduced submission package.

1. *Conditional Approval*[2]: This procedure is applicable when there is a complete pharmaceutical and pre-clinical data package and an almost complete set of clinical data, if it is considered reasonably likely that the remaining data will be collected in a short timeframe. To qualify, a product must be intended for treatment, prevention or diagnosis of a seriously debilitating or life-threatening disease; have designated orphan status; or

[2] COMMISSION REGULATION (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council.

be intended for use in emergency situations, responding to European Community or WHO recognised health threats. Conditional approval is valid for one year on a renewable basis.

2. *Exceptional Circumstances Licensing*[3]: This is used when it is assumed that comprehensive data can never be provided, for example because the disease is too rare, the scientific knowledge is too limited, or because of specific ethical constraints in that it would be unethical to submit seriously ill patients to extensive tests.
3. *Accelerated Assessment*[4]: This procedure is designed to meet the legitimate expectations of patients and to take account of the increasingly rapid progress of science and new therapies. It applies to medicinal products of major interest from the point of view of public health and therapeutic innovation. An application for an accelerated assessment procedure must justify that the medicinal product will be of major public health interest. Based on the request, the justifications presented, and the recommendations of the rapporteurs, the Committee for Medicinal Products for Human Use (CHMP) will formulate a decision. Such a decision will be taken without prejudice to the CHMP opinion (positive or negative) on the granting of a marketing authorisation.

These examples demonstrate that there is regulatory interest in trying to explore novel options for assessing safety and getting innovative therapies into the clinic, but again these are often piecemeal and seen as the exception rather than the norm. Considering the limitations of conventional animal models for regenerative medicine testing, regulators may be willing to explore innovations in regulatory science that would enable good quality in vitro data to play a greater role in early stage proof of concept and safety. New approaches in practice and standards, approved for different types of regenerative medicine therapies, would enable such regulatory innovations to become the norm rather than the exception and this could reduce uncertainty and facilitate clinical translation. However, such change will require regulators and policymakers to embrace alternative approaches and normalise a regenerative medicine-specific approach to regulation.

The Bloodpharma project has the potential to deliver a high-value commercial product that pushes the boundaries of both science and regulation, if the manufacturing/scale-up challenges can be overcome and the regulatory path to a successful demonstration that the product is safe and effective in the niche thalassemia market can be met. Despite the complexity and uncertainty associated with the development of the cultured blood product and concerns about the viability of regulatory routes to market, the successful completion of each milestone does cumulatively increase the potential commercial viability of the product. For example, the Bloodpharma team are succeeding in addressing some of the technical questions that seemed so challenging at the beginning of this project in 2010:

[3] Guideline on Procedures for the Granting of a Marketing Authorisation under Exceptional Circumstances, pursuant to Article 14(8) of Regulation (EC) No 726/2004 (EMEA/357981/2005).

[4] Guideline on the Procedure for Accelerated Assessment, Pursuant to Article 14(9) of Regulation (EC) No 726/2004.

This is one example of how RM products are very different from conventional pharmaceuticals and many biologics as manufacturing and scale-up capacity is directly shaped by regulatory decisions or, in many cases, uncertainty about appropriate protocols. As Williams [7] points out, there is today a much greater appreciation of the way in which business models, production systems, and approaches to managing the regulatory burden of manufacturing are closely intertwined. He notes that regulators have a difficult task in balancing risk and therapeutic benefit with the challenge of validating GMP manufacturing: 'A key part of determining a cost-effective manufacturing strategy for a regenerative medicine product is to understand the interplay between alternative manufacturing solutions, business models, their associated regulatory burden and risk in all its dimensions.' [7; p. 68]. The Bloodpharma team can be seen as trying to design optimal manufacturing processes to clinical grade GMP standards and to align them with this uncertain and changing regulatory pathway. These factors render the complexities, uncertainties and costs of R&D for such products far more significant than for conventional therapies, with relatively well known and understood manufacturing processes and supply chains.

One suggestion for expediting translation of RM therapies to the clinic, in the context of regulatory challenges, is to promote more structured industry-academic collaboration and pre-competitive cooperation [46]. However, valuable as such an approach might be, a much more flexible and adaptive regulatory and governance framework, beyond piecemeal attempts to streamline regulatory processes and modify some regulatory science protocols, would have the greatest and most positive impact on the clinical translation of RM.

In the case of the Bloodpharma project and similar types of allogeneic therapy, we have identified innovative regulatory science coupled with more flexible and bespoke regulatory approaches as initiatives that could facilitate innovation whilst maintaining the highest standards for safety and efficacy of the therapy. This would be in the interests of companies developing innovative therapies and of regulatory organisations. Products such as cultured blood will continue to push the boundaries of science, technology and regulatory regimes. This article has mapped and described some of the critical points where the science and manufacturing pathways could benefit from greater flexibility in regulatory requirements.

The role of methodological innovation in supporting the development of RM technologies

In parallel with the innovative character of the science and technology contributing to the development of the cultured blood product, the REALISE project [2] was the test bed for a new approach to the analysis and foresighting of business models and product development pathways for advanced innovative technologies. The methodological innovation that underlies Figs 1–4 of this paper proved to be effective in analysing the complex and uncertain innovation pathways for new RM products, helping those developing the product to plan better in the face of future scientific, regulatory and funding uncertainties. It is now leading to the development of a framework of analytic methods and guidelines to enable the analyst to shift focus from the

development pathways envisaged by companies and scientists, to the regulatory and governance systems being developed by policy makers, or to the agendas of stakeholders and third sector actors.

Most of the evidence available to date on the factors that support or inhibit innovation, across the board, comes from the key actors in the process–the companies, regulators, or other stakeholders, each of whom has a vested interest in a particular set of outcomes and each therefore contributing their particular biases to the case they make. It is particularly important to have independent analyses, as described in this paper, in support of better decision making by all involved in innovation processes.

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